

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Generic Name: Ultrasound Bone Sonometer

Device / Trade Name: OSTEOSPACE

Applicants name and address: MEDILINK
80, rue de l'Hortus
34280 CARNON
France

Applicant's U.S. Representative: Michael Manolagas
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Dedham, MA 02026

Dates of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P010058

Date of Good Manufacturing Practice Inspection: February 28, 2002

Date of notice of approval to the Applicant:

II. INDICATIONS FOR USE

The OSTEOSPACE is a quantitative ultrasound bone sonometer device (QUS) to be used for the measurement of broadband ultrasound attenuation (BUA) of the calcaneus, as an aid, together with other clinical risk factors, to diagnose osteoporosis and other medical conditions leading to reduced bone strength and to estimate the risk of subsequent atraumatic fracture. The output is expressed in terms of BUA, T-score, and Z-score.

III. CONTRAINDICATIONS

None.

IV. WARNINGS and PRECAUTIONS

See attached device labeling.

V. DEVICE DESCRIPTION

OSTEOSPACE (Ultrasound Bone Sonometer) is an electrically operated quantitative ultrasound (QUS) bone sonometer which measures bone properties at the calcaneus using non-audible high-frequency sound waves. The device consists of the scanner, dedicated PC and accessories. The scanner consists of a footwell to position the foot and two ultrasound transducers that contact the heel so that ultrasound beam is passed through it. The minimum specifications for the computer are : Pentium 3 or better processor with at least 800MHz operating speed ; Windows 98, 2000, or XP operating system ; 128 Megabytes memory ; 20 Gigabytes disk memory ; and a main board with parallel output (LTP1). The accessories: keyboard, mouse, compatible printer and monitor (15'' or bigger) can be supplied by the customer, distributor or MEDILINK.

The OSTEOSPACE is controlled directly by a dedicated computer. All instructions and examination results are maintained in the computer, along with a software version of the User Manual. OSTEOSPACE allows the possibility to back-up the results onto disk. Printed reports of the examination results are produced using an external printer.

The results are given as Broadband Ultrasound Attenuation (BUA) in dB/MHz. This ultrasound parameter is based on the frequency dependent attenuation, with the higher BUA values corresponding to lower risk of fracture, and vice versa.

Before the BUA measurement can be used for a diagnosis it needs to be compared to the average value of the young normal Caucasian female. This comparison is done using an index called T-score, which represents the BUA value on a normalized scale. T-score above (below) 0 corresponds to a bone stronger (weaker) than that of the average young normal Caucasian woman. The T-score is the recommended parameter for assessing the risk of fracture.

Comparing the actual BUA value to the average value in a healthy population of the same gender, ethnic origin, and age, when expressed in terms of standard deviations (SDs) of that population, is called Z-score, which can be used as an aid in the detection of conditions associated with non-age-related bone loss.

An OSTEOSPACE examination includes the following steps: probe positioning, soft tissue thickness calculation, examination and processing operation. The OSTEOSPACE measurements are made with the patient seated in a chair with his/her foot placed in the footwell of the scanner. The heel is smeared with standard water-soluble ultrasound gel; the gel is the medium for the transmission of ultrasound. The transducers are positioned with the aid of a low power laser onto the external part of the malleolus. The transducers are then brought into contact with the heel. A transducer on one side of the heel converts an electrical signal into a sound wave which passes through the patient's heel. The second transducer on the opposite side of the patients' heel receives the sound wave and converts it into an electrical signal that is analyzed by the OSTEOSPACE software. An infrared beam positioner allows reproducible positioning to the same Region of Interest (ROI) for repeat examinations. The probe positioning occurs when the patient has placed their foot into the footwell, and the measurement length of the foot size is entered into the computer software. The low powered laser light is moved into position onto the external maleolus by the operator. The computer thus ensures that the probes are correctly

positioned to obtain the ROI of the calcaneus. This can be further verified by the operator. The soft tissue thickness calculation of the patient's heel is made by the transmission and detection of the reflected wave.

Examination of the patient lasts several seconds. During this period, 20 consecutive ultrasound measurements are made on the foot, followed by the computer calculation of the broadband ultrasound attenuation (BUA) of the Region of Interest (ROI).

The quality of each examination can be verified by the operator in comparing the ultrasound signal displayed at the end of the examination on the computer monitor. The patient details, including laser / probes positioning are recorded on the computer to ensure continued follow-up of patient examinations and greater precision in repeat measurements.

VI. ALTERNATIVE PRACTICES & PROCEDURES

Alternative methods for assessing bone status include single energy x-ray absorptiometry (SXA), dual energy x-ray absorptiometry (DEXA), quantitative computed tomography (QCT), single photon absorptiometry (SPA), and dual photon absorptiometry (DPS). Of these techniques, SXA, DEXA and SPA have been used specifically for the estimation of Bone Mineral Density (BMD) of the calcaneus. These established techniques estimate BMD at a variety of anatomical sites, including the heel, by measuring the attenuation of x-rays due to passage through the bone. In addition, there are several bone sonometers that are currently being marketed for assessment of a patient's skeletal status (fracture risk).

VII. MARKETING HISTORY

OSTEOSPACE has been commercially available in markets outside the United States since 1997. Two hundred eighty (280) units have been sold in over 35 countries world-wide, including Europe, Latin America, Asia and the Middle East.

No OSTEOSPACE has ever been withdrawn from any market due reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

None known.

IX. PRE-CLINICAL STUDIES

A. Electrical Safety

MEDILINK verified compliance of the OSTEOSPACE with the general safety requirements of IEC 60601-1: 1996 and the electrical safety requirements of IEC 60601-1-1:1996.

B. Electromagnetic Compatibility

MEDILINK verified compliance of the OSTEOSPACE with the electromagnetic compatibility requirements of IEC 60601-1-2: 1996 (EMC Directive 89/336/CEE).

C. Ultrasound Acoustic Evaluation

MEDILINK tested the physics of the 4 ultrasound transmitting/receiving probes in accordance with the Track 1 of the Food and Drug Administration's (FDA) 510k guidance, entitled "Measuring and Reporting Acoustic Output of Diagnostic Ultrasound Medical Devices", 1985 (Table 1). Acoustic levels were well below acceptable pre-amendment values.

	Probe 1	Probe 2	Probe 3	Probe 4	Typical uncertainty (+/-)
MI	0.068	0.070	0.069	0.064	12%
P_{r3} (MPa)	86×10^{-3}	88×10^{-3}	87×10^{-3}	81×10^{-3}	10%
I_{SPPA} (W/cm ²)	0.40	0.45	0.47	0.43	27%
ISPTA (mW/cm ²)	4.2×10^{-3}	4.4×10^{-3}	4.3×10^{-3}	4.1×10^{-3}	25%
Beam diameter (cm)	7.0	6.5	6.1	7.4	6%

Table 1-Acoustic Output Values

D. Software

OSTEOSPACE is classified as Minor Level of Concern device (Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 29, 1998). Software hazard risk analyses demonstrated that all hardware, software and user concerns were adequately addressed. Verification, validation and unit testing demonstrated that the device operates in a manner as described in the specifications.

E. Biological / Sterility

The patient contact materials used in the OSTEOSPACE are ones which have been used in the medical field without any known adverse effects or reactions. No additional testing was required, since the safety of the contact materials was well established.

The labeling instructs the user to clean the footwell with a disinfectant between patients. The labeling provides specific instructions on how to ensure the effective use of the disinfectant.

FDA-cleared water soluble ultrasound gel contains chemicals known in the medical field and provides no risk to the patient. No additional testing was deemed necessary.

X. SUMMARY OF CLINICAL STUDIES

Clinical studies were conducted to assess the safety and effectiveness of the OSTEOSPACE, a quantitative ultrasound bone sonometer device, as an aid to establish the diagnosis of osteoporosis and to identify patients with high risk of osteoporotic fracture. Clinical studies were carried out in two U.S. centers, the University of Massachusetts (UMASS) and the University of California (UCSF), San Francisco, and in one European center, the Geneva University Hospital (HUG), Switzerland. The same protocol was followed in all the centers.

A. Reference Database Study

Objective: This study was to establish a U.S. Reference Database (Normality curve) for the BUA of OSTEOSPACE on healthy or non-fractured Caucasian U.S. women aged 20 to 79 (Reference Database Study).

Methods: Four hundred ten (410) healthy Caucasian U.S. females, ranging in age from 20 to 79 years, were measured using the OSTEOSPAC5 to establish the normality curve.

Results: BUA was found statistically independent of age for 235 females ranging from 20 to 47. Thus, over this period, the reference curve could be represented as a constant equal to the average BUA over the group ($BUA_{20-47} = 66.16$ dB/MHz). Over 47 years old, a 3rd order polynomial regression was found to fit the best.

Conclusions: The Normality Curve of OSTEOSPACE BUA for Caucasian U.S. Women displayed in Figure 1 shows that between the age of 48 and 60 years (post menopause), the BUA significantly declined by 3.5 dB/MHz (approximately 83% of the total range). Then, from 60 and 79 years old, the BUA further declined by 0.7 dB/MHz, i.e. approximately 17% of the range.

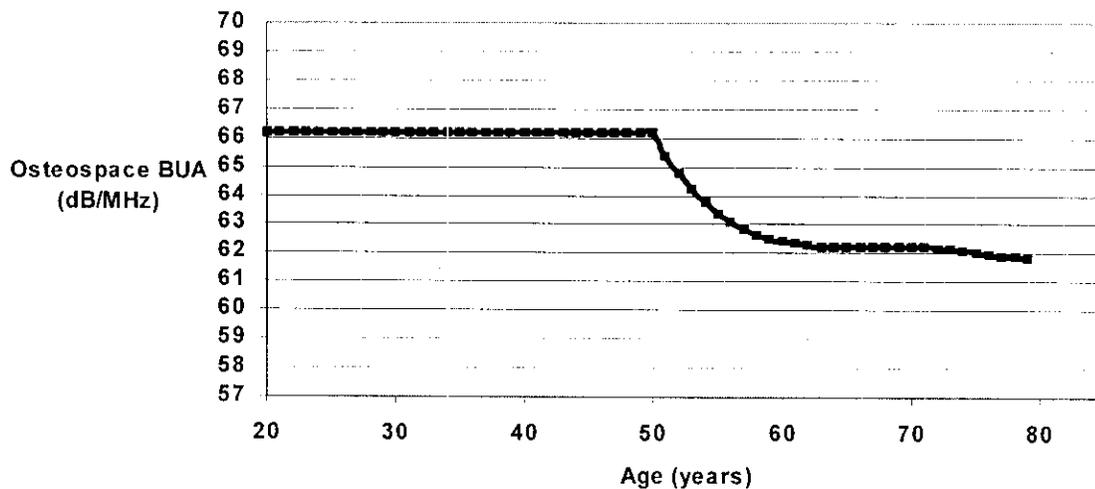


Figure 1- Normality Curve of OSTEOSPACE BUA for Caucasian U.S. Women

The World Health Organization (WHO) criterion for T-score is the difference between the patient’s measurement and the mean of a healthy young female Caucasian reference population between the ages of 20 and 39 expressed as the number of standard deviations, for the reference database, between the two values. The reference population for this device shows that there was no difference between using 20-39 group and 20-47 group. However, the 20-39 age range was selected for the representative sample of the young normal Caucasian U.S. female reference population to maintain consistency with the WHO definition. This young reference population’s mean BUA, as well as its standard deviation (SD), were calculated for the purpose of generating T-scores (see Table 1).

	Value (dB/MHz)	95% Confidence Interval
Mean BUA OSTEOSPACE	66.16	65.5 - 66.8
Standard Deviation	4.6	3.8 - 5.4

Table 1- Young Reference Value for OSTEOSPACE BUA (Data From 171 U.S. Caucasian Females, Ages 20 to 39)

Given the previous results, the T-score of the patient “j” is calculated as follows:

$$T\text{-score}_j = \frac{BUA_j - 66.16}{4.6} \quad \text{where } BUA_j \text{ is the BUA measured on the patient "j".}$$

B. Precision Study

Object: To estimate the in-vivo short-term precision of the BUA obtained by OSTEOSPACE (Precision Study) f

Methods: Fifty-six (56) subjects ranging in age from 20 to 79 were recruited by UMASS and UCSF the two U.S. centers and used to assess the measurement reproducibility. Each subject was examined three times with OSTEOSPACE, with foot repositioning before each examination.

Results: Precision was evaluated by calculating the RMS SD (Absolute Precision), the RMS CV(Relative Precision), the CV, the SCV(Standardized Coefficient of Variation) and the TSD(Standard Deviation of the T-score). (See section 17 of the User Manual for definitions). Results are displayed in Table 2.

BUA OSTEOSPACE	
RMS SD	1.19dB/MHz
RMS CV	1.84 %
CV	1.31 %
SCV	3.97 %
TSD	0.26

Table 2- Results of the Evaluation of the OSTEOSPACE Precision (56 American Subjects Aged between 20 to 79)

Conclusions: The CVs for the OSTEOSPACE measurements show that the device can provide precise measurements of BUA.

C. Fracture Risk Studies

Object: To establish the capability of OSTEOSPACE BUA, a) to assess the risk of fracture, b) to discriminate between patients who have suffered atraumatic fractures and age-matched control subjects who have never had an atraumatic fracture, and c) to compare the performance of the device with those of one DEXA (Hologic QDR 4500[®]) and two sonometer systems (Lunar ACHILLES+[®] and Hologic SAHARA[®]), in order to assess possible bias in selection of control patients ("Fracture Risk Studies"). The output of the QDR 4500 is bone density. The output of the ACHILLES+[®] is Stiffness and the SAHARA[®] is the Quantitative Ultrasound Index (QUI).

Methods: In order to assess the capacity of OSTEOSPACE to evaluate the risk of fracture and to discriminate the Osteoporotic patients, fractured subjects and age-matched controls were enrolled by the HUG and UCSF centers. UCSF measured 52 age-matched controls and 50 fractured patients. HUG measured 43 age-matched controls and 56 fractured patients. Subjects were measured using the OSTEOSPACE (both sites), Hologic QDR 4500[®] (UCSF only), Lunar ACHILLES+[®] (HUG only) and the Hologic SAHARA[®] (HUG only).

Results: Table 3 shows that the BUA results for the fractured group expressed in T-score or in Z-score are similar to neck or spine BMD.

	Controls	Fractured	Z-score	T-Score
BUA OSTEOSPACE	62.6 ± 4.5	58.8 ± 4.9	-0.9	-1.6
Neck BMD (QDR 4500 [®])	0.695 ± 0.111	0.614 ± 0.111	-0.7	-2.1
Spine BMD (QDR 4500 [®])	0.960 ± 0.145	0.839 ± 0.141	-0.8	-1.9

Table 3- UCSF Center, OSTEOSPACE and DEXA Parameters of the Two Groups Expressed in Z-score and T-score

Table 4 shows that the OSTEOSPACE measurements for the fractured subjects, when expressed in T-score or in Z-score, are similar to the QDR 4500[®] neck or spine BMD, or to Hologic QUI and Lunar Stiffness results.

	Controls	Fractured	Z-score	T-Score
BUA OSTEOSPACE	61.2 ± 5.0	55.8 ± 5.2	-1.1	-2.3
QUI (SAHARA [®])	73.9 ± 15.3	59.8 ± 19.4	-0.9	-2.2
Stiffness (ACHILLES+ [®])	71.0 ± 11.3	58.6 ± 12.5	-1.1	-1.8

Table 4- HUG Center, OSTEOSPACE and QUS Parameters for the Two Groups Expressed in Z-score and in T-score

For each center, non-adjusted and adjusted Odds Ratios per standard deviation decrease were estimated, with their 95% confidence intervals, and the areas under the ROC curves were obtained (see Tables 5 and 6).

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA OSTEOSPACE	2.44 (1.49 - 3.98)	1.80 (1.05 - 3.10)	0.72 (0.62 - 0.82)
Neck BMD (QDR 4500 [®])	2.30 (1.40 - 3.79)	1.70 (1.02 - 2.99)	0.71 (0.60 - 0.81)
Spine BMD(QDR 4500 [®])	2.47 (1.53 - 3.98)	2.32 (1.36 - 3.93)	0.74 (0.64 - 0.84)

*Adjusted by Age, Weight and Height.

**Not Adjusted by age.

Table 5- UCSF Center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA OSTEOSPACE	3.04 (1.81 - 5.10)	2.91 (1.57 - 5.37)	0.77 (0.68 - 0.86)
QUI (SAHARA [®])	2.47 (1.46 - 4.17)	1.88 (1.05 - 3.34)	0.77 (0.68 - 0.86)
Stiffness (ACHILLES+ [®])	3.17 (1.83 - 5.47)	2.56 (1.39 - 4.73)	0.77 (0.68 - 0.86)

*Adjusted by Age, Weight and BMI.

**Not Adjusted by age.

Table 6- HUG Center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters

Conclusions: ROC curves as well as Odds Ratios analysis showed no statistical difference between OSTEOSPACE, DEXA, and QUS measurements, thus demonstrating the absence of any significant bias in selection of control patients, and also demonstrating the ability of the OSTEOSPACE to discriminate between fractured subjects and controls.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

A. Safety

The safety of OSTEOSPACE has been demonstrated during the clinical evaluation, with no reports of adverse events or side effects. This clinical experience is consistent with the worldwide experience with OSTEOSPACE.

B. Effectiveness

The results of the clinical studies demonstrate that both the capacity of OSTEOSPACE BUA to discriminate between osteoporotic and non-osteoporotic subjects and its ability to assess risk of fracture are comparable with those of BMD obtained by DXA absorptiometry technique. BUA measured by OSTEOSPACE has a comparable precision to other QUS systems. Therefore, OSTEOSPACE can be used as an aid to diagnosing osteoporosis and to determining the risk of subsequent atraumatic fracture.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiologic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on MAR 15 2004

The applicant's manufacturing facility was inspected on February 28, 2002, and was found to be in compliance with the Quality Systems regulations.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions in the attached labelling.

XV. REFERENCES

General References:

[1] Glüer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. *Osteoporos Int* 1995;5(4):262-70.

[2] CG Miller, RJ Herd, T Ramalingam, I Fogelman, GM Blake Ultrasonic Velocity Measurement Through the Calcaneus: which velocity should be measured, *Osteoporosis Int* , 1993. 3.31-35

[3] Glüer CC, How to characterize the ability of diagnostic technique to monitor the skeletal changes. *Journal of Bone and Mineral Research* 1997; 12: S378.